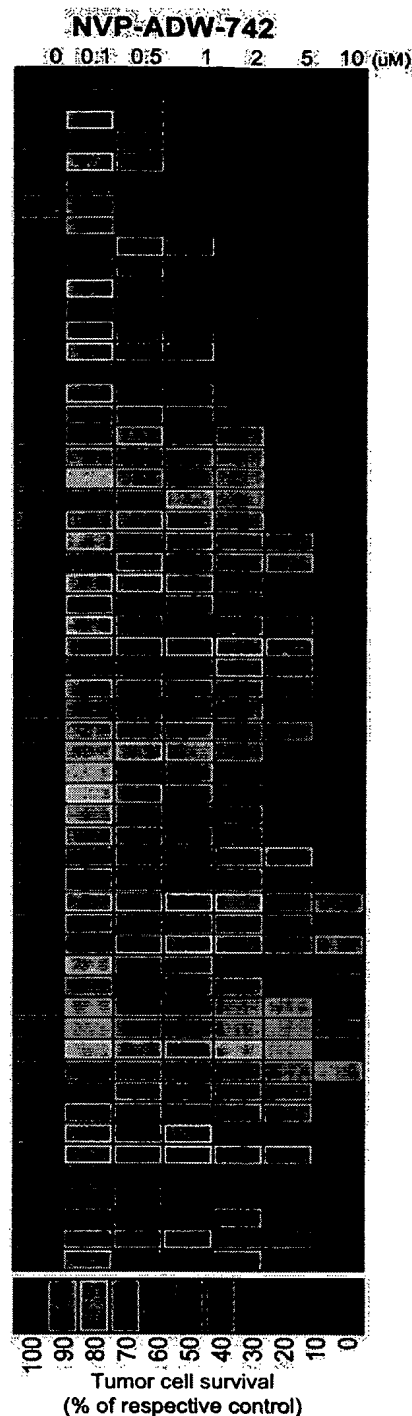


e

Cell lines tested:

- INA-6
- ARD
- NCI-H929
- ARK
- L363
- MM-1S-Bcl-2
- LP-1
- MM-1S
- MM-1S-myr-Akt
- MM-1R
- OPM-1
- EJM
- OCI-My5
- MM-1S-TR-15
- KMS-12-BM
- RPMI-8226/S
- U266
- MR20
- OCI-My7
- LR5
- Brown
- Dox40
- XG-1
- LR5
- DHL-10
- DHL-4
- DHL-7
- DHL-8
- RL
- WM-WSU
- GDM-1
- HL-60
- KG-1a
- REH
- BHP-10
- BHP-17
- BHP-2
- SW-579
- TT
- WRO
- ARO
- FRO
- ZR-75-1
- MCF-7
- MDA-MB-231
- PC-3
- LNCaP
- DU145
- 786-O
- ACHN
- SW480
- SKOV-3
- TC106
- TC71
- TC268
- TC248
- WERI



A	Control
B	αIR3
C	NVP-ADW742
D	anti-IL-6R
E	20% serum
F	αIR3+20%serum
G	NVP-ADW742+20%serum
H	anti-IL-6R+20%serum

Figure 2

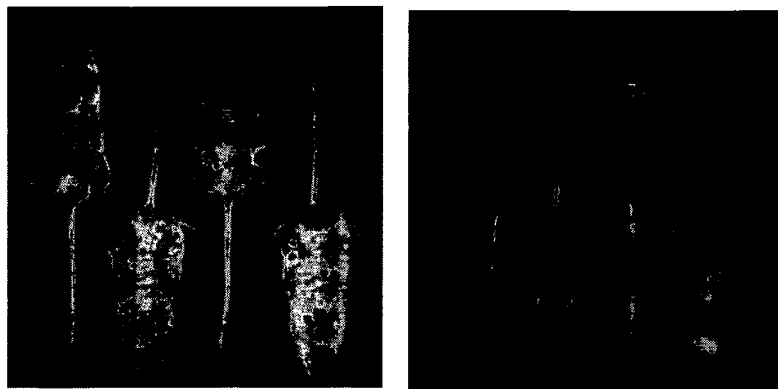
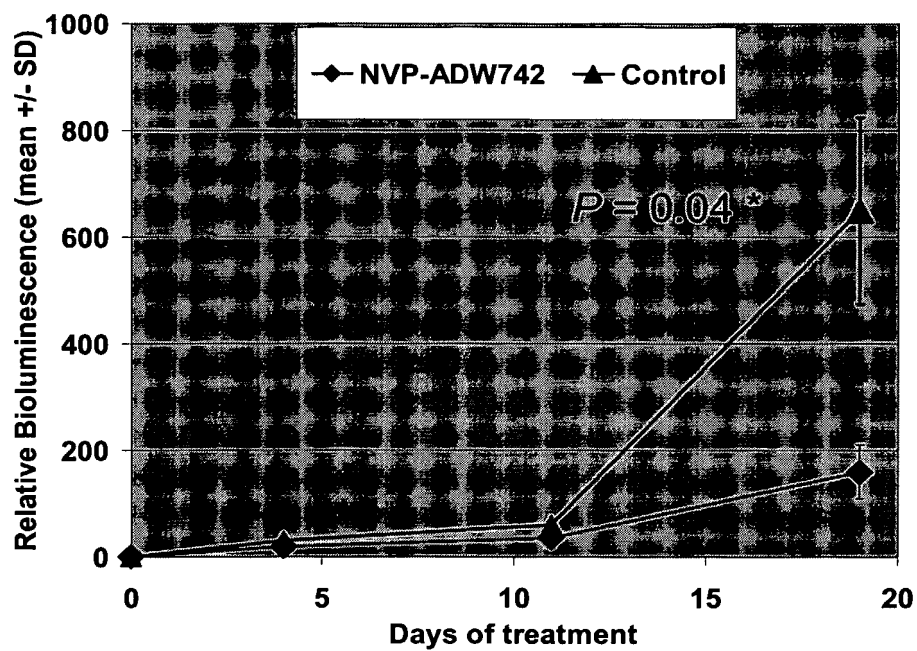
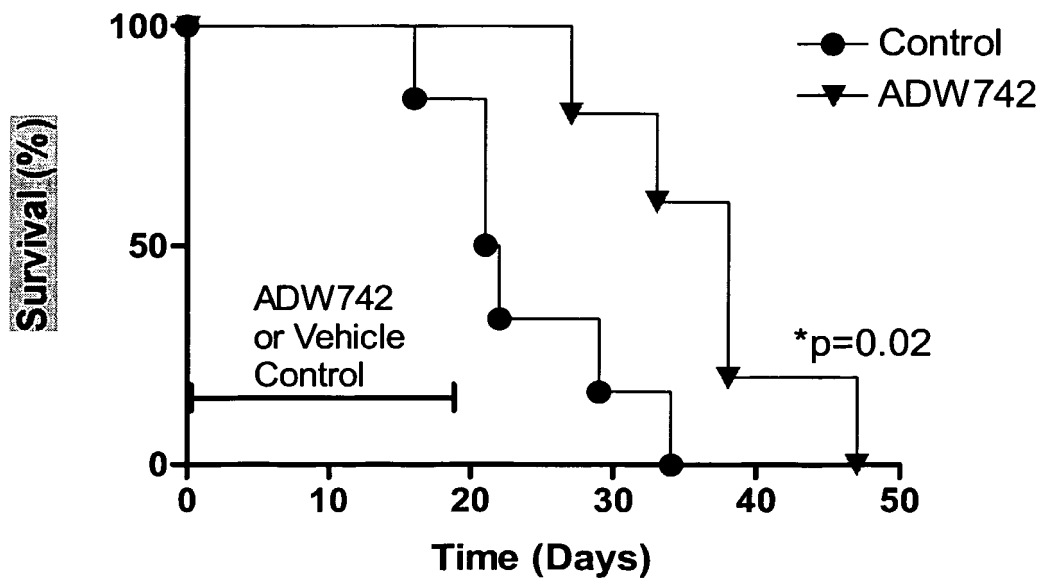
a*b**c*

Figure 3

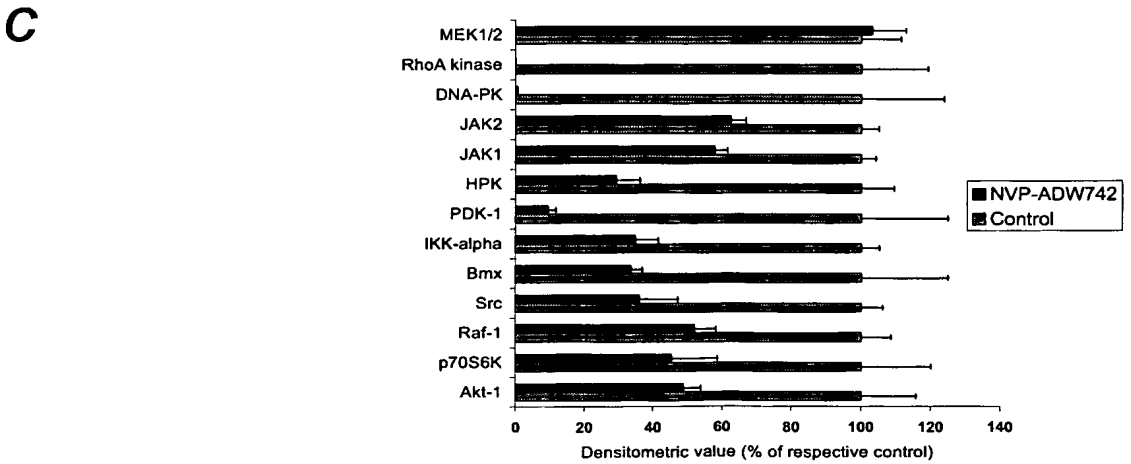
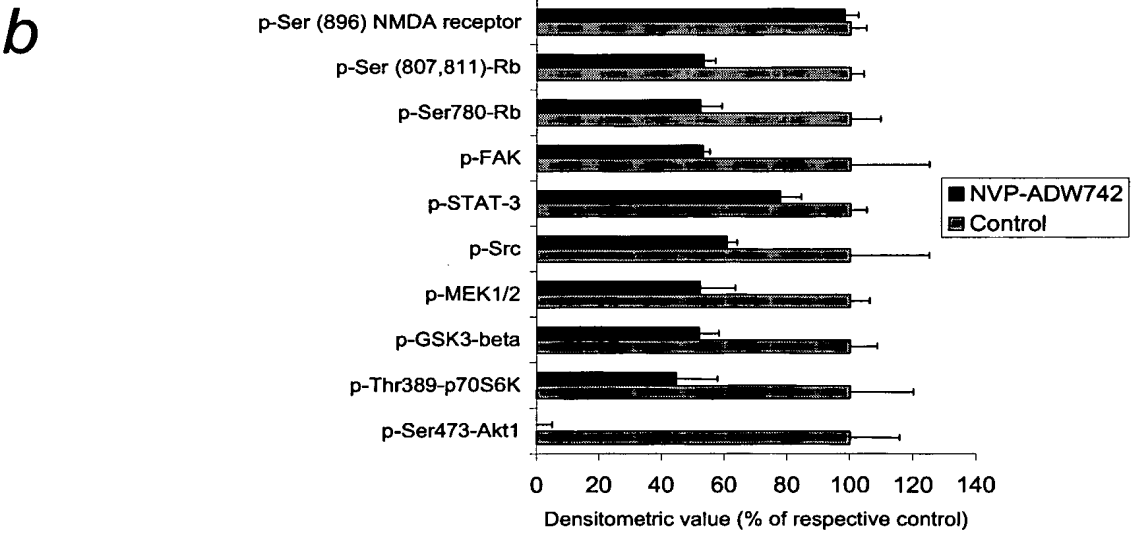
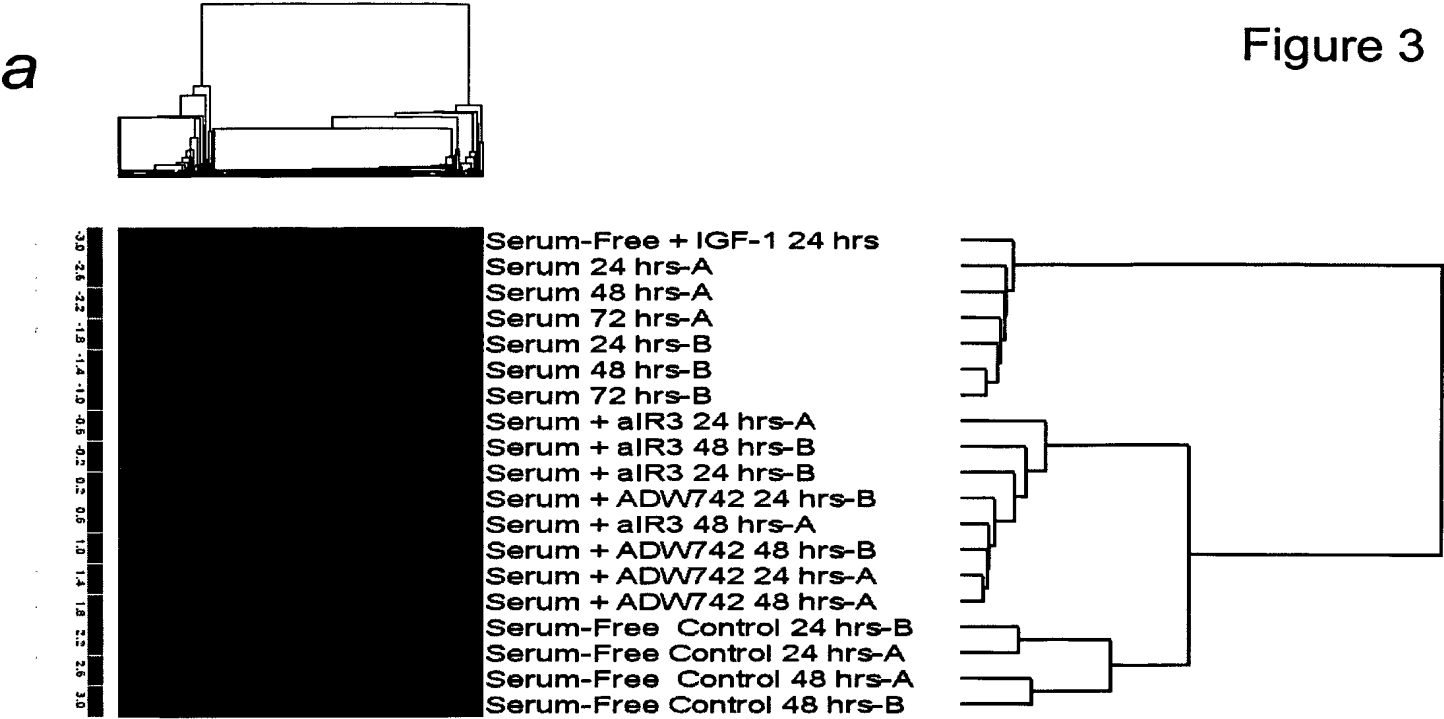


Figure 4

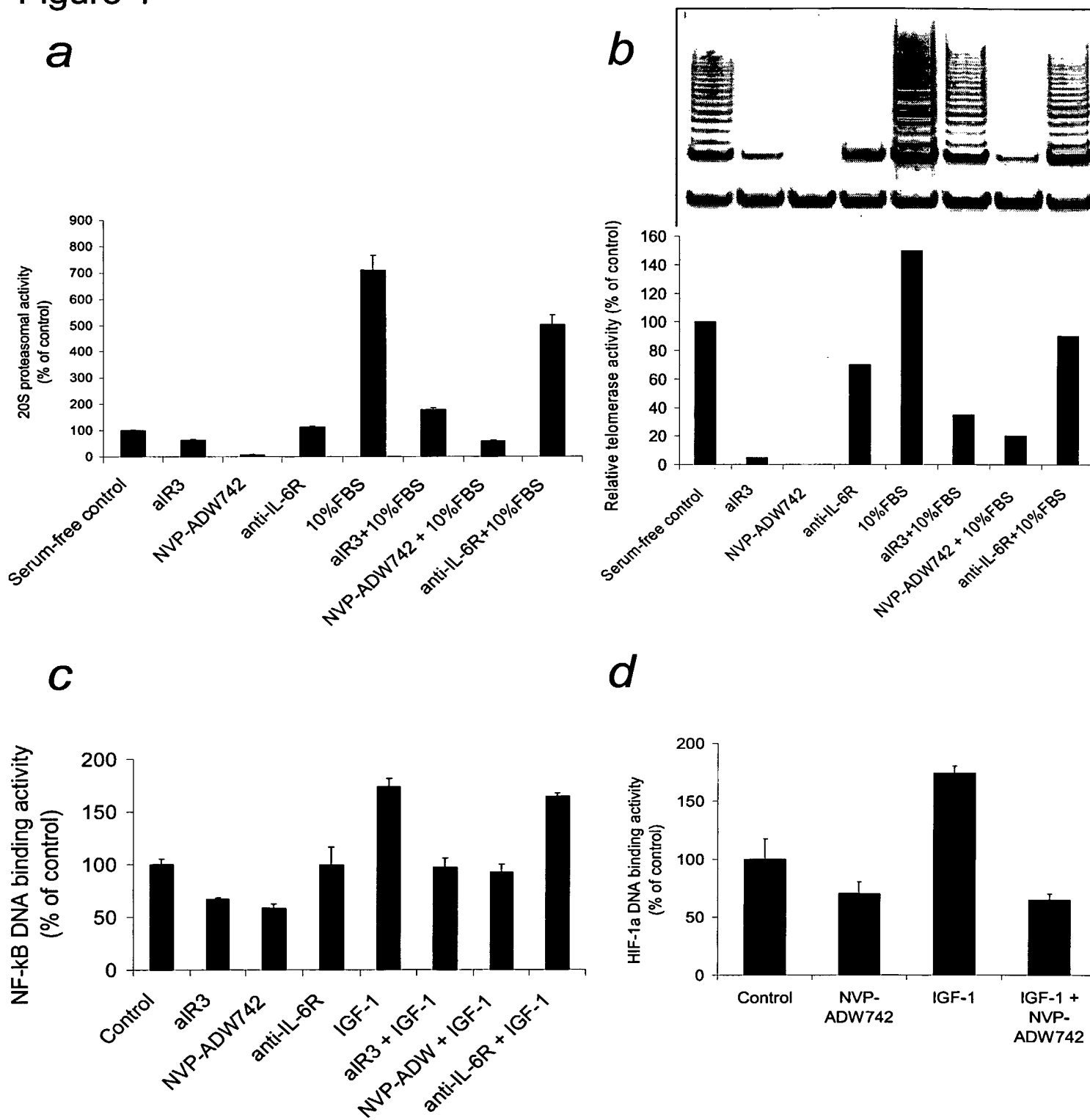


Figure 5

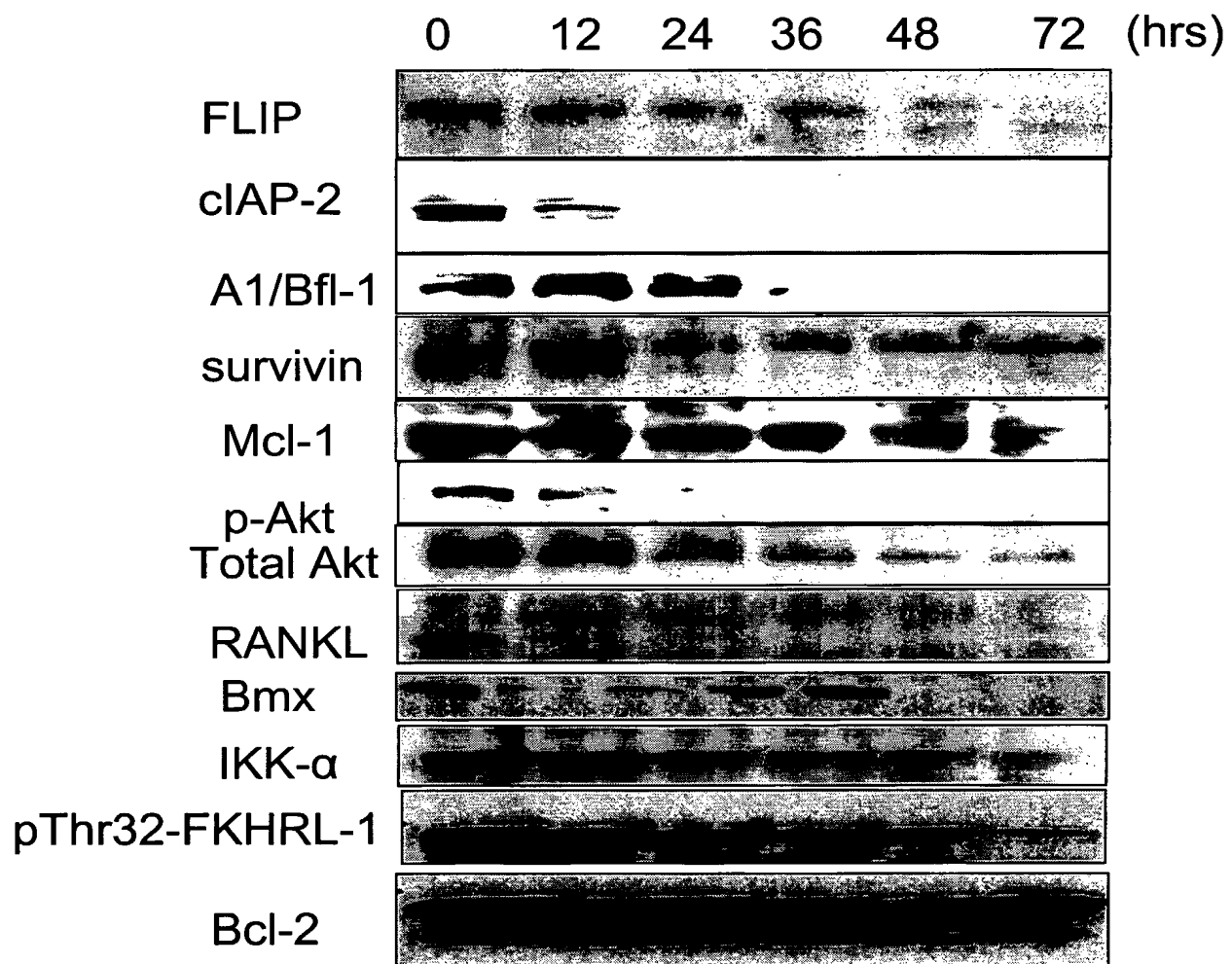


Figure 6

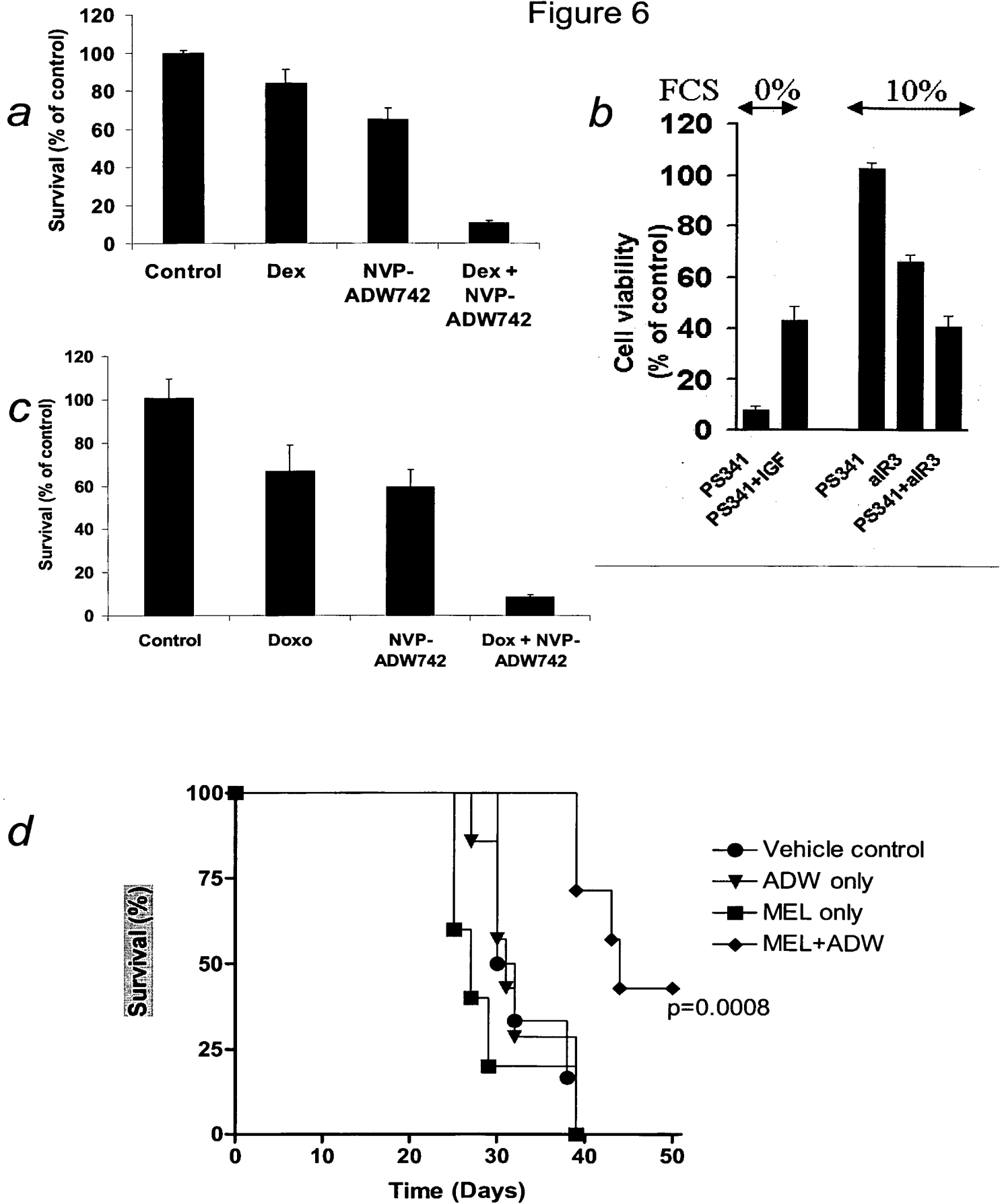


Fig 7

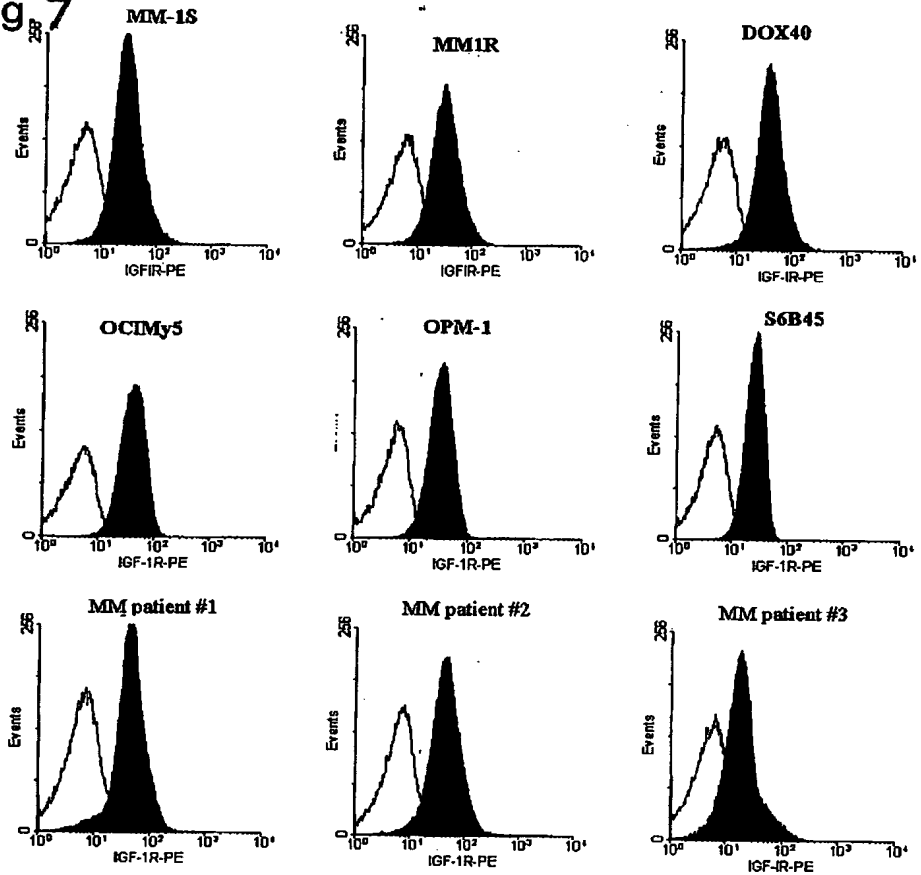
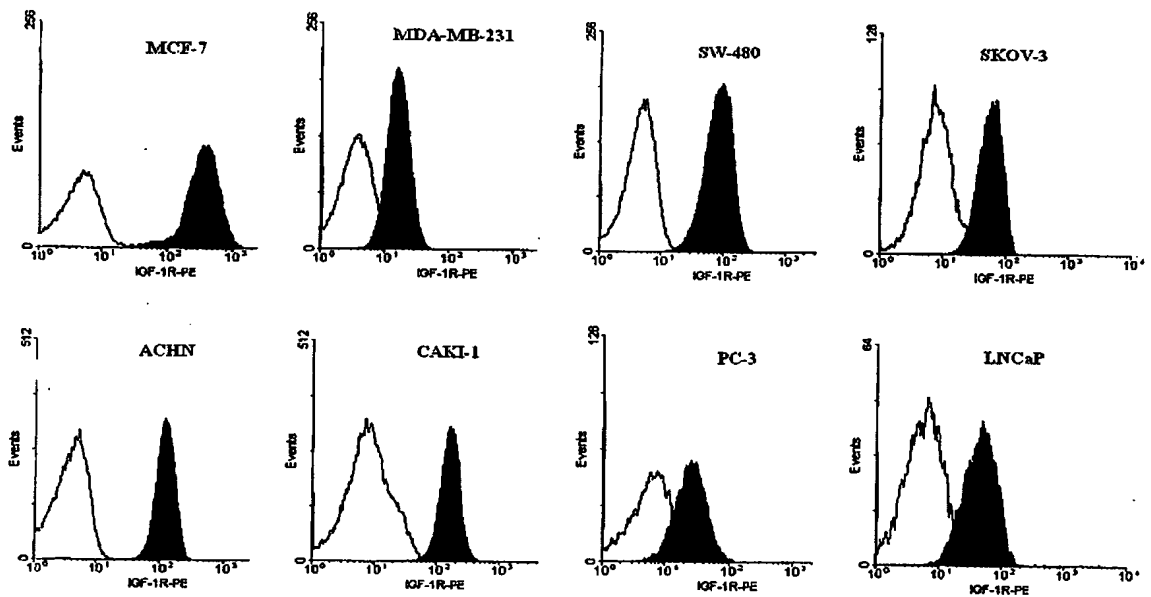
a*b*

Figure 8

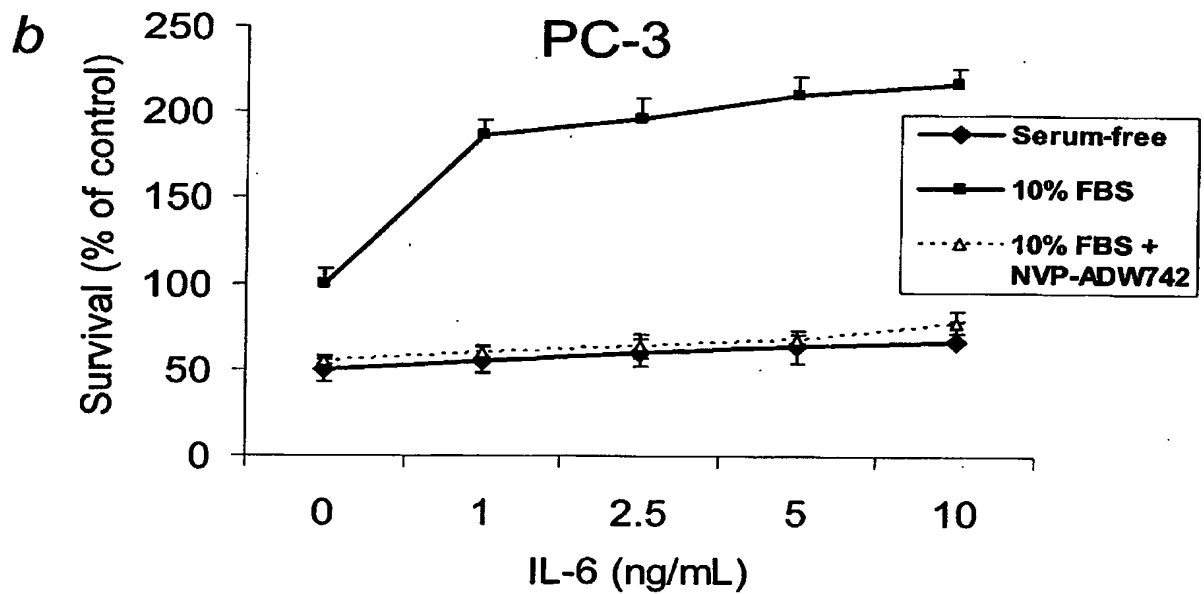
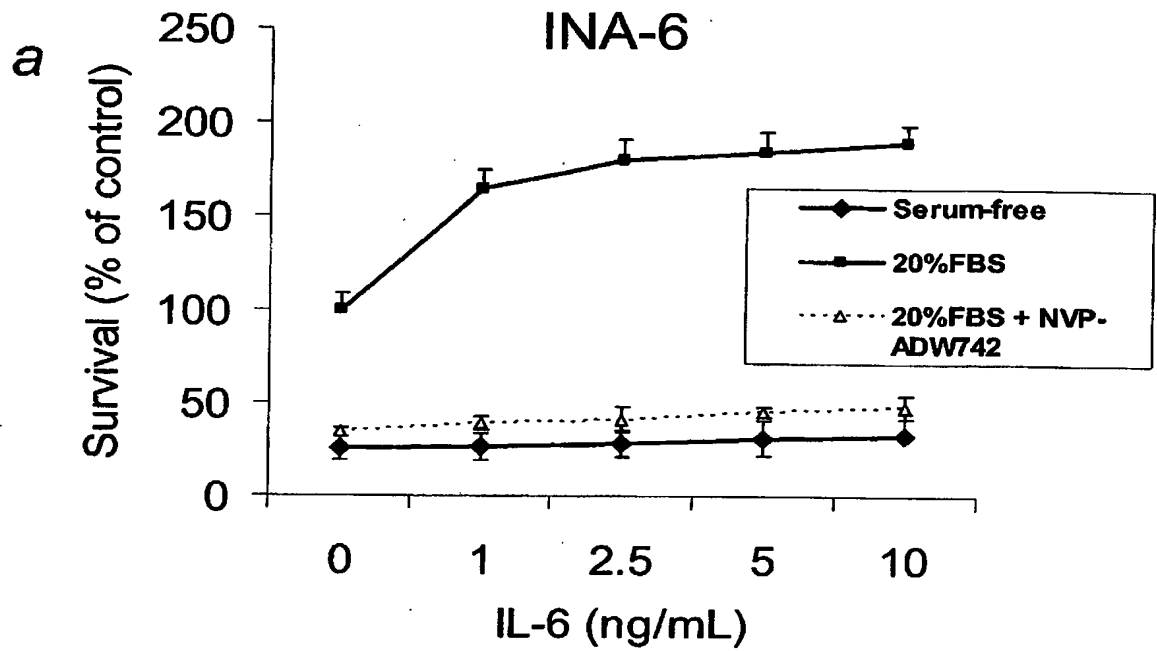


Fig. 9

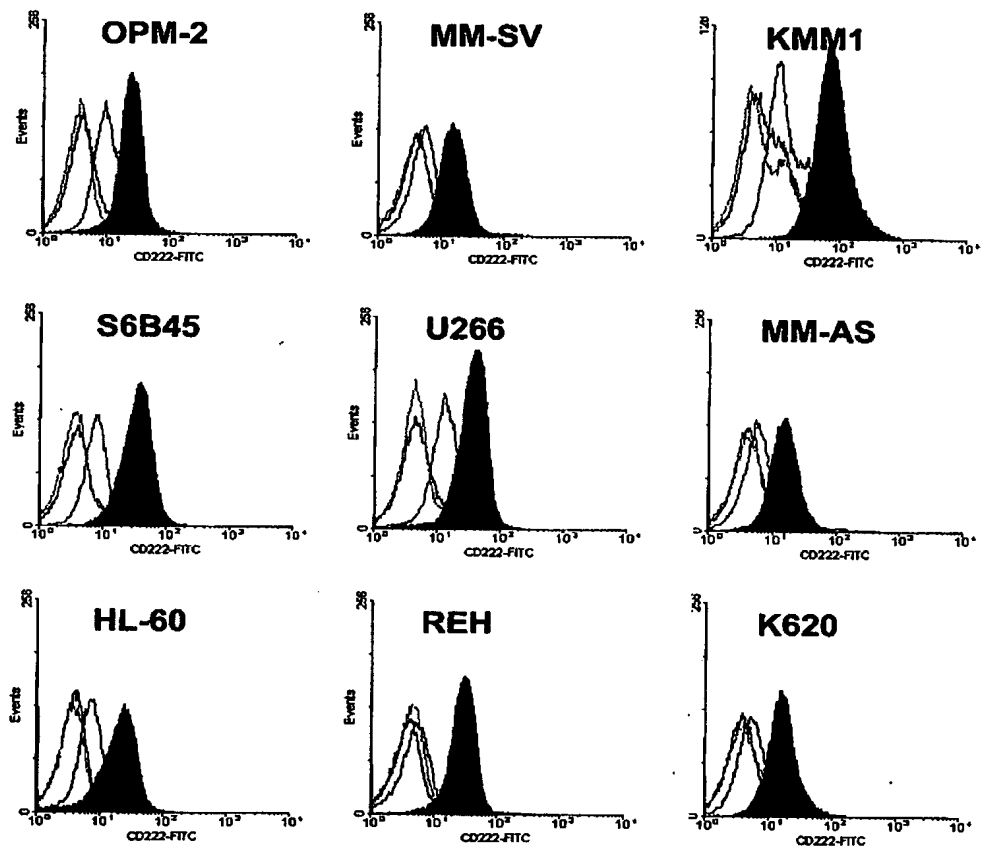


Figure 10

Transcriptional signature of IGF-1 stimulation

	Upregulated	Downregulated
Cell signaling	CK-1 and -2, chemokine-like factor 1, CXCR-4, Aurora-1, Aurora-2, SAK, SGK, PP2A, some PP1 subunits, PP4, GADD- α and - β , PTEN, CD71	FLIP, c-raf1 (but upregulated at protein level), Gas6, IGF-1, IGF-1R, IGF-2R, IFN- α , b, omega receptor, IL-2R γ , gp130, RAR- α , RAR- γ , BCMA, TNF- α -induced protein
Apoptosis regulation	Survivin, Bad, PCD5, PCD8, PCD10, VDAC3	Bcl-2 (no effect on protein level on short- to mid-term stimulation), Mcl-1 (stable protein levels), TOSO
Cell cycle control	Ki-67, CDC -2, -5, -6, -7, -20, -23, -25, -28, -45, cyclins A2, B1, B2, E1, F, G1, (D1, D2, D3), CDK2, CDK4, PCNA, replication factor C (multiple subunits), replication proteins A1, A2, and A3, ASK, CHK1, G2-S-expressed 1, stathmin/oncoprotein 1, Wee1+	
Microenvironmental interactions	RHAMM, Integrin α E, ADAM-8, -22, -28	Integrin α 8, α L, β 1, β 5
Wnt signaling pathway		Frizzled-related protein, WNT10B, WNT5B
Transcriptional/translational control	ATF-1, ATF-3, E2F-3, eIF-1, -2, -3, -4 and -5, multiple ribosomal proteins, DP-1, c-myb, XBP-1	c-myc
DNA synthesis/repair enzymes	BUB1, BUB3, DNA-PK, deoxycytidine kinase, deoxythymidylate kinase, DHFR, dyskerin, dUTP pyrophosphatase, MCM 2, 3, 4, 5, 6, 7, MSH-2, -3, -6, RAD51, guanine monophosphate synthase, RRM1, RRM2, TOPBIIA, XRCC	
Histone regulation	HDAC1, HAT1	
Oncogenes	DEK, liposarcoma fusion gene t(12;16), SET translocation	
Heat shock proteins / Chaperones	Hsp90, -70, 105, 27, 110, 14-3-3, chaperonin TCP1	
Immune system interactions		MHC class IE and II (less extensive changes in comparison to IL-6 or co-Cx)
Nucleocytoplasmic transport and other carrier proteins	Exportin, nucleoporins 50, 54, 62, 88, 98, 155, karyopherins b1, b3, a1, a2, a3, a4, kinesin-like 1, 2, 4, 5, 6, 7 (multiple Rab, Ran proteins), transportins	
Metabolism	FOF1 ATPase mitochondrial, ornithine decarboxylase, HMG-CoA reductase, calmodulin-1 and -2	
Ubiquitin/Proteasome pathway	POH, Multiple 26S subunit genes (26S subunits α 1, α 2, α 3, α 5, α 7, β 1, β 2, β 3, β 5, β 6, β 7, β 8, ATPase 1,2, 3, 4, 5, 6, non-ATPase 1, 2, 4, 7, 8, 11, 12, 13), UCEs, USPs	Some USPs (-9, -11)

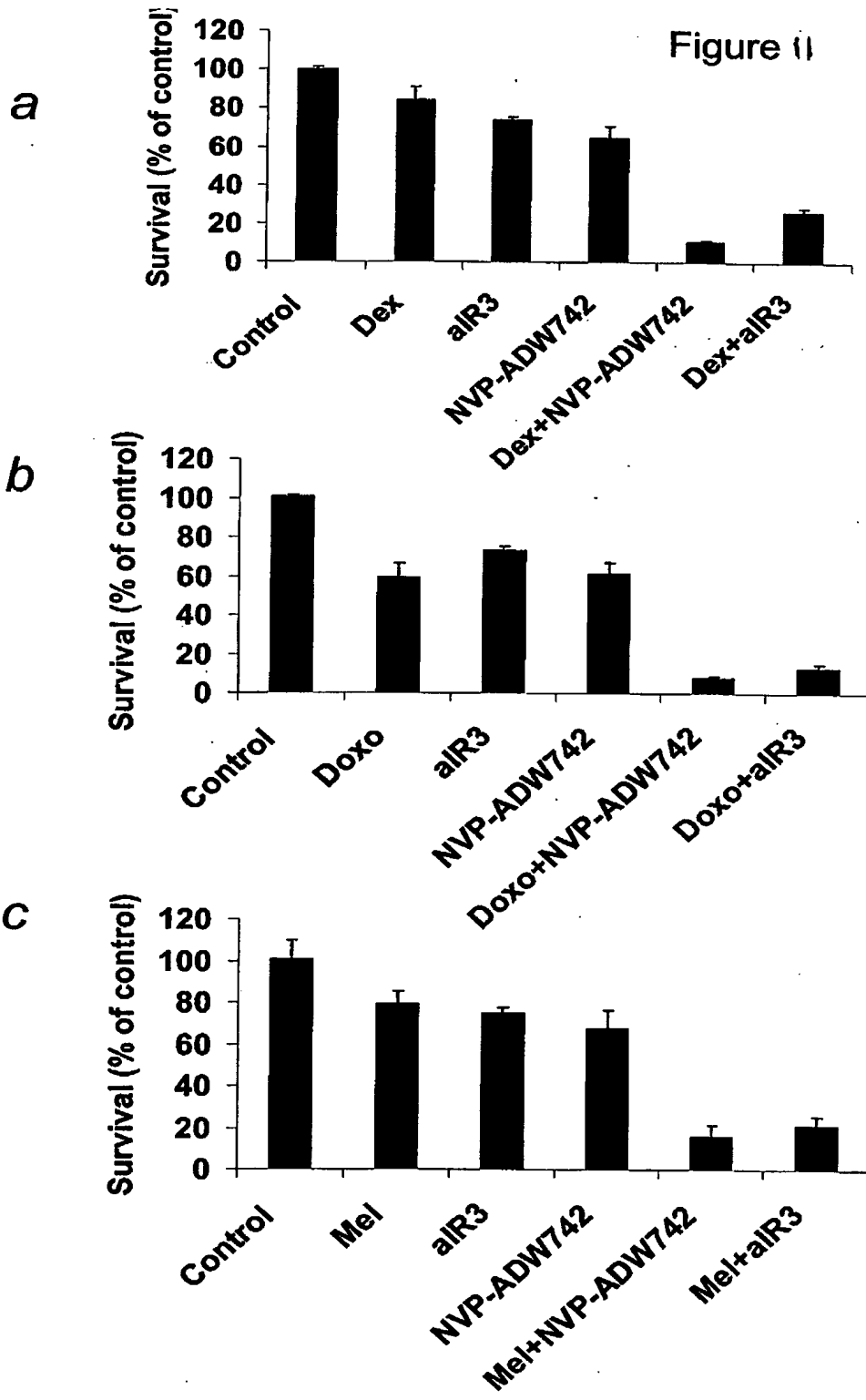


Figure 12

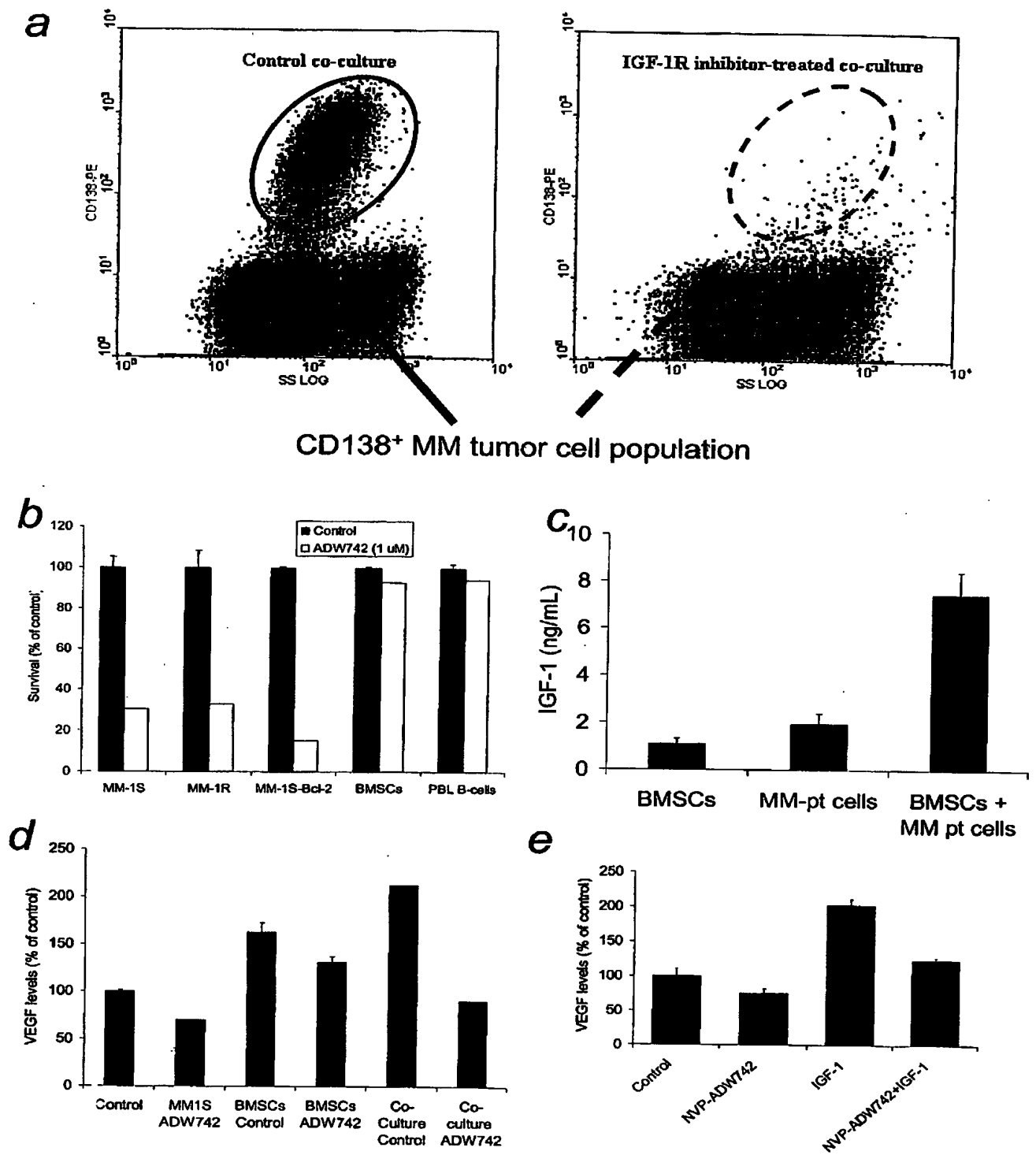


Figure 13

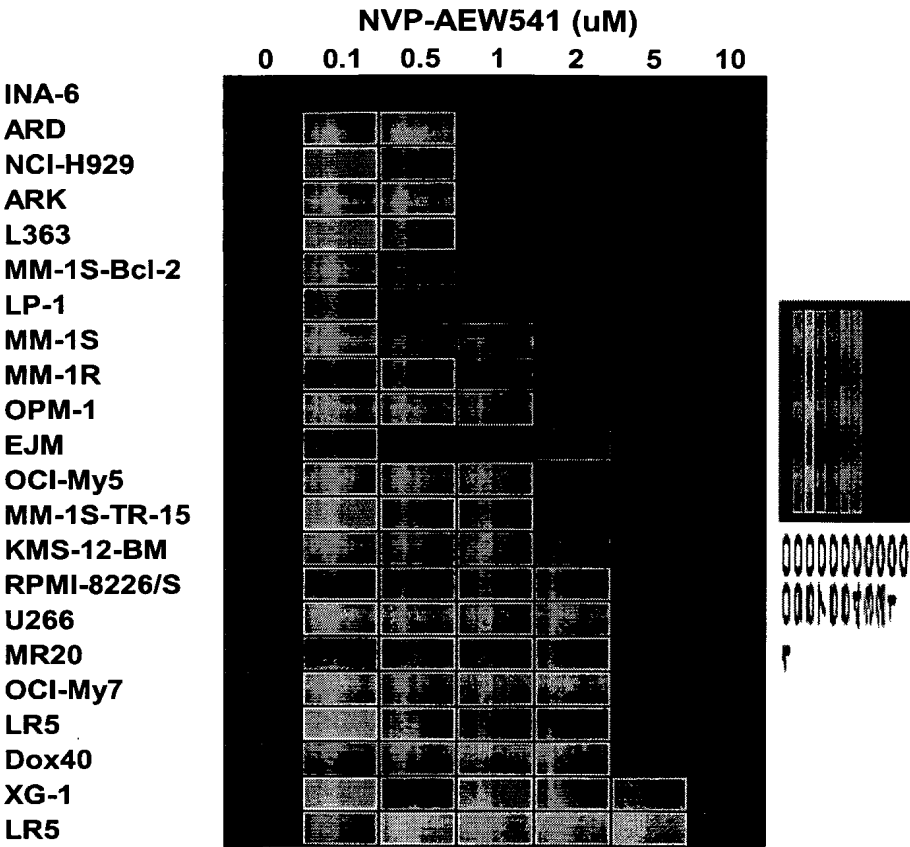


Figure 14

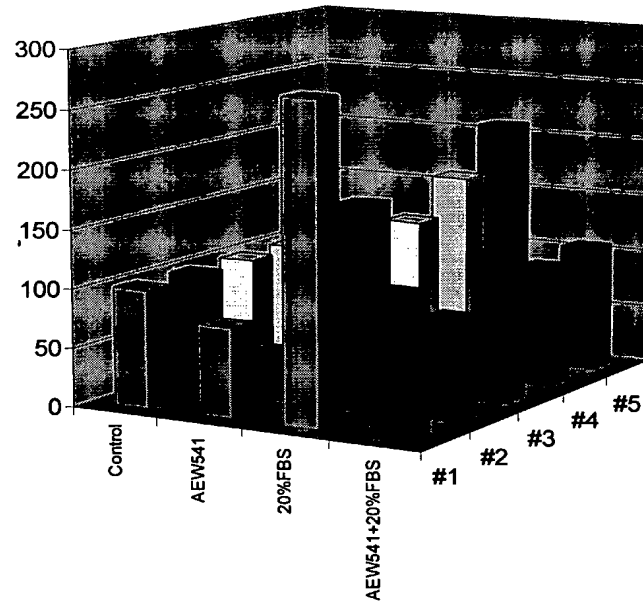


Figure 15

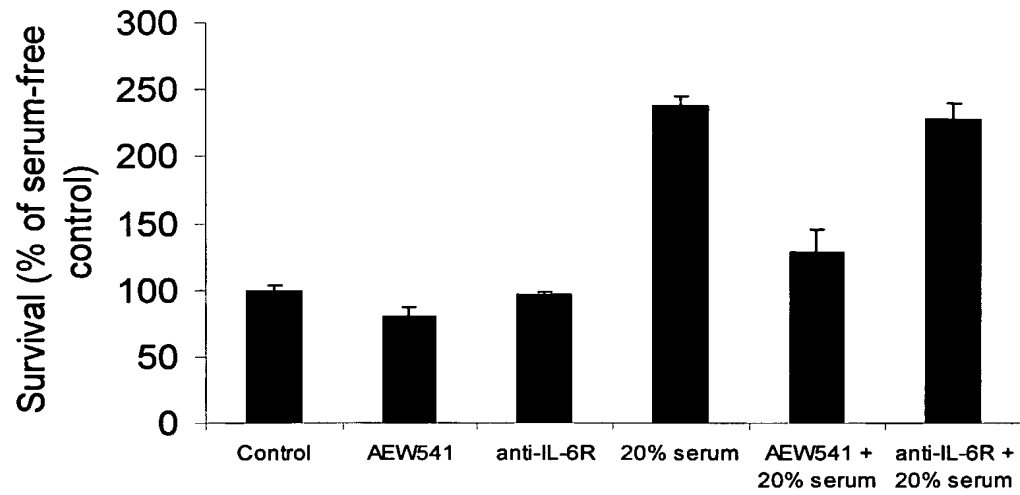


Figure 16

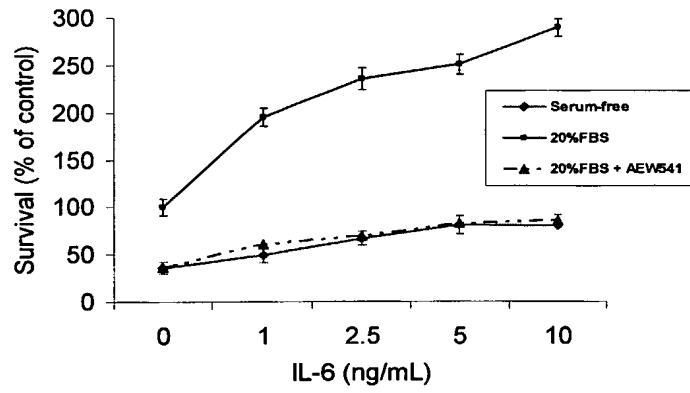


Figure 17

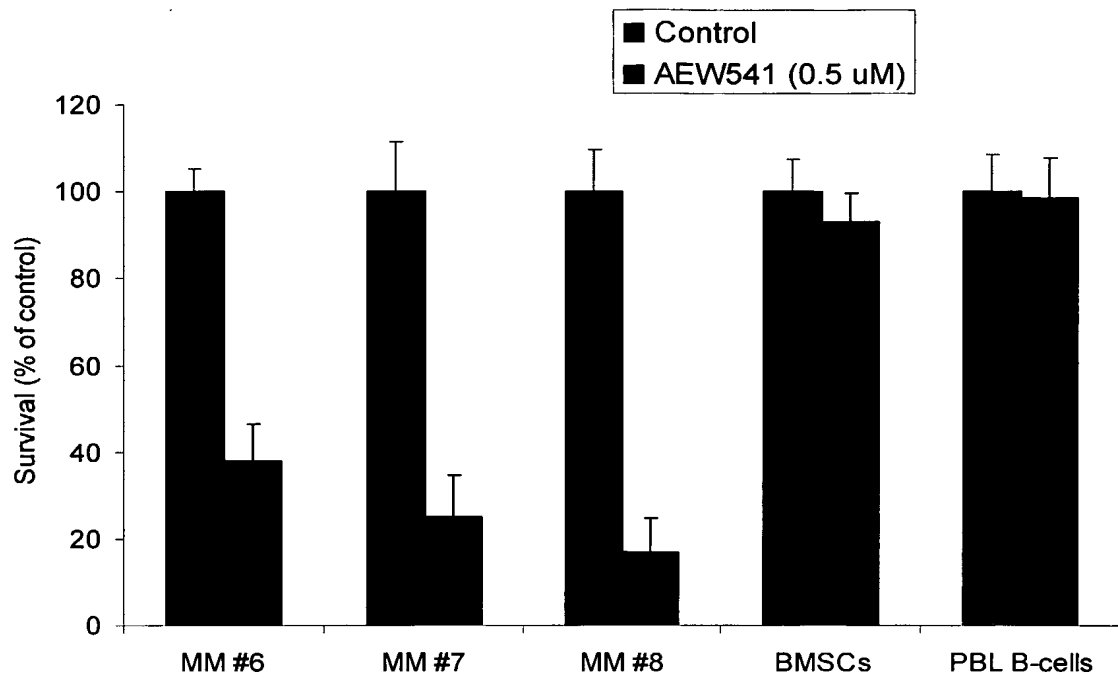


Figure 18

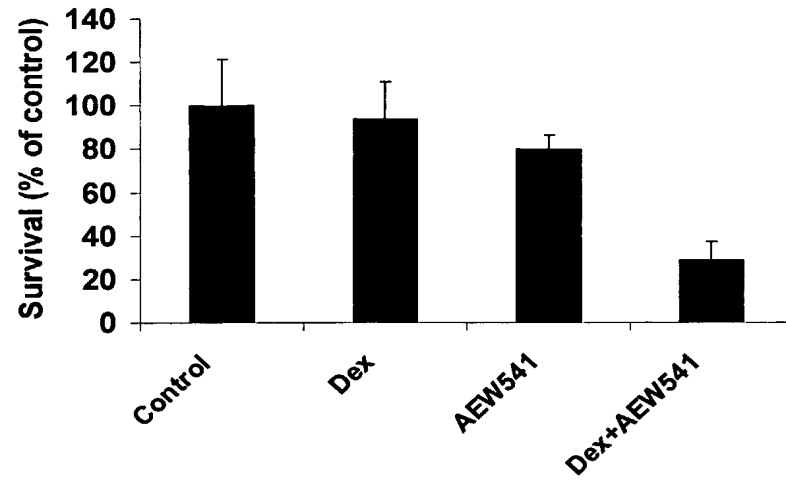


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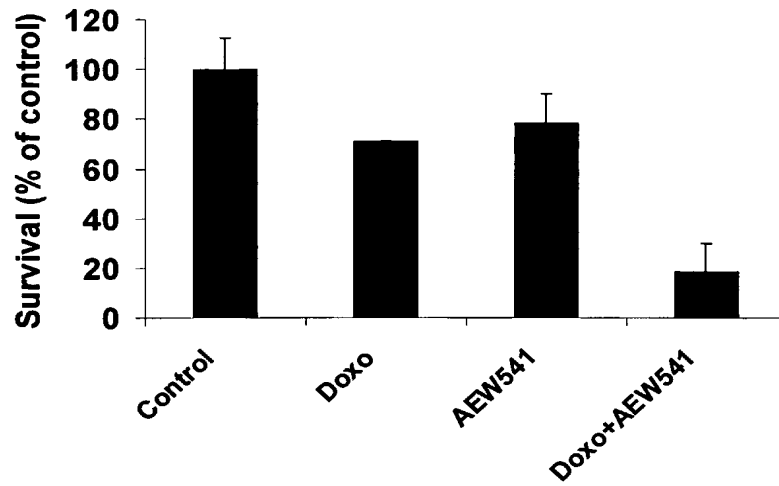
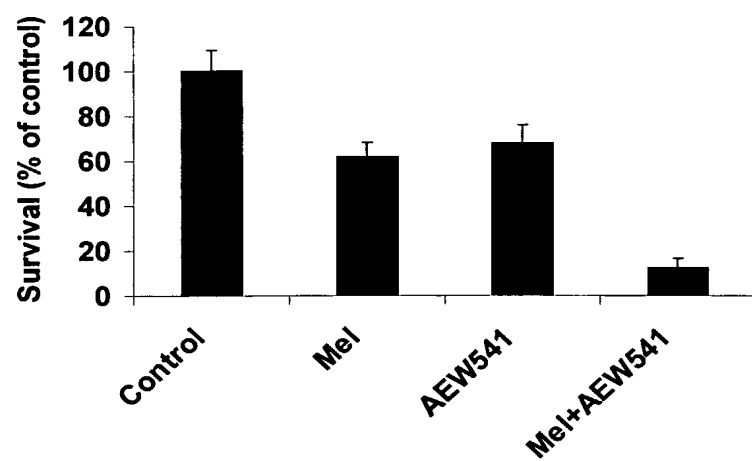


Figure 20



21/30

21/30

Figure 21

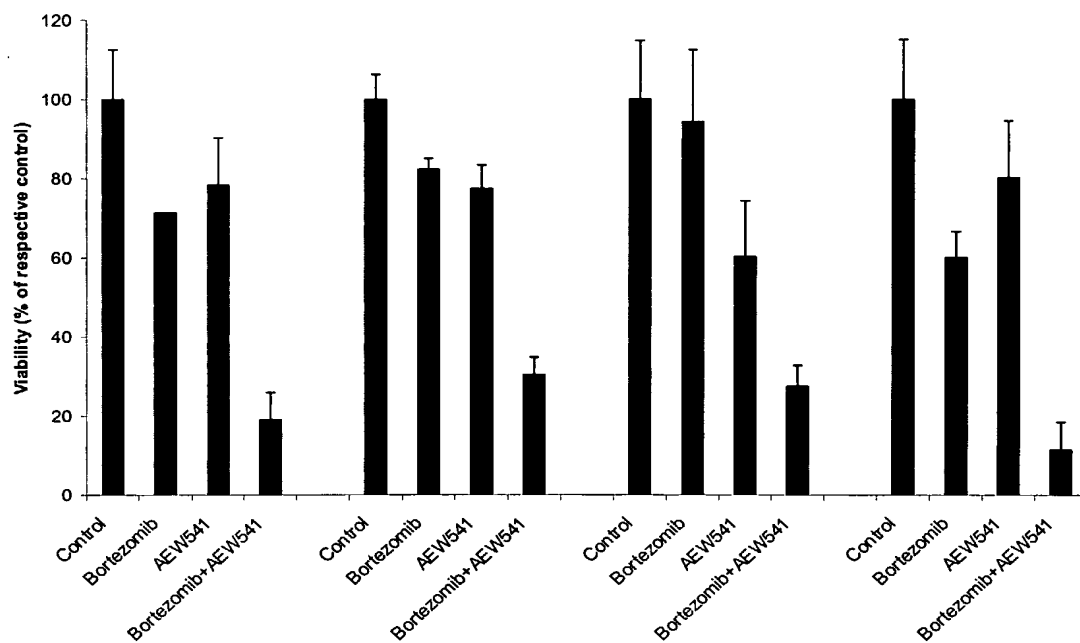


Figure 22

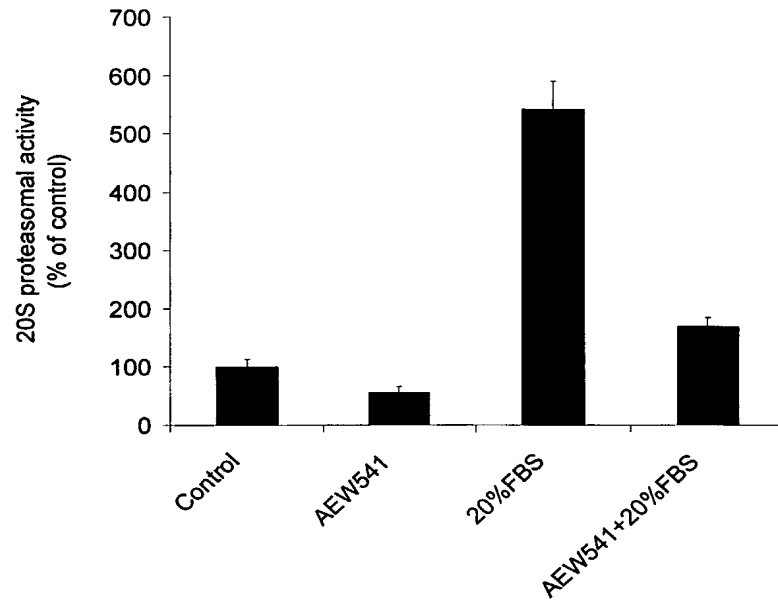


Figure 23

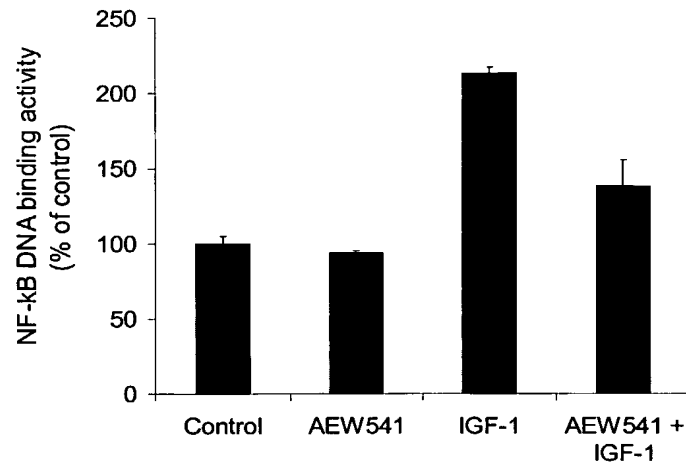


Figure 24

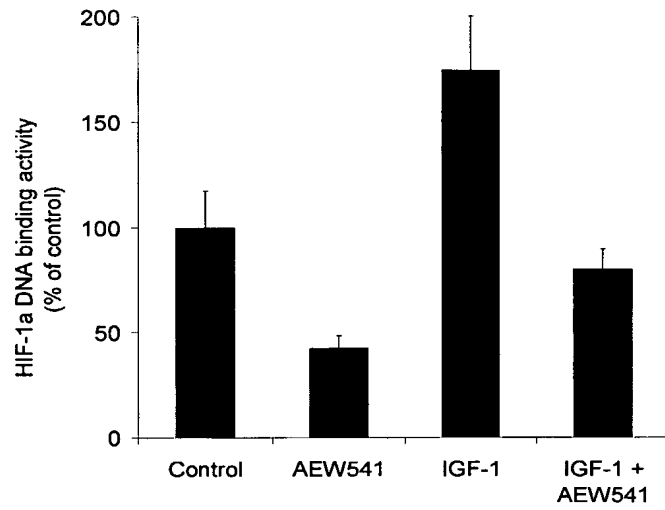


Figure 25

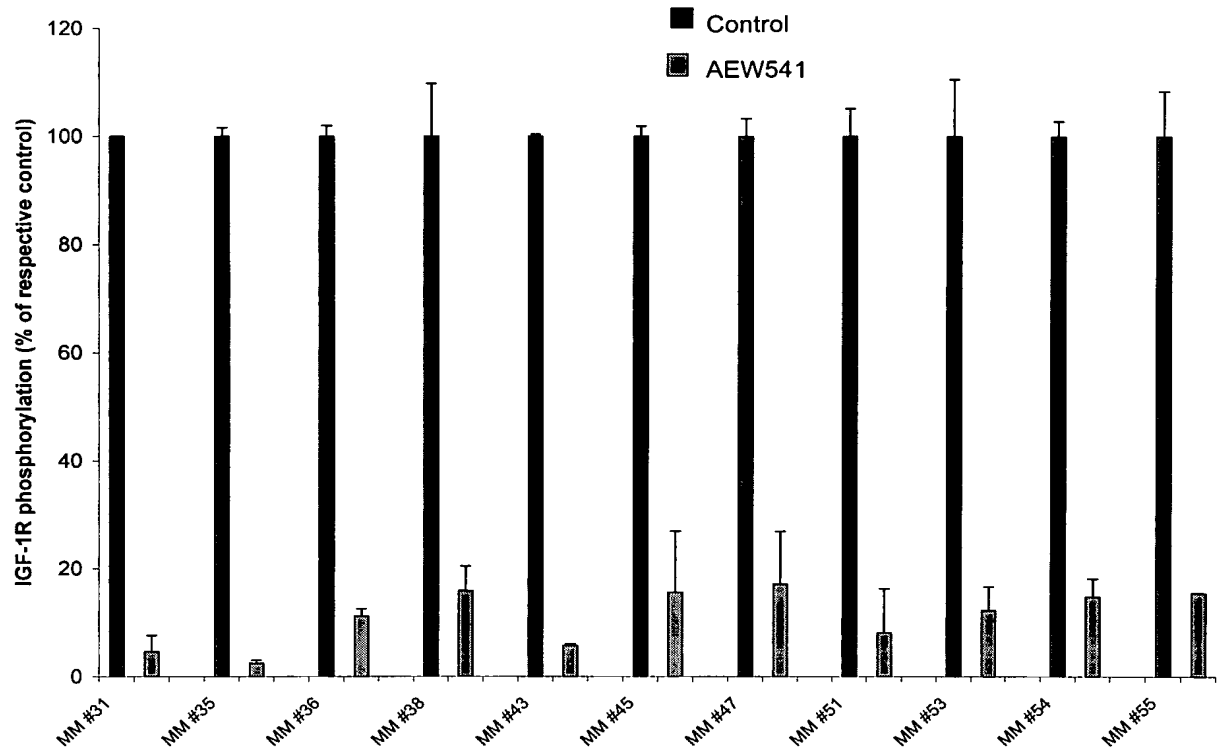
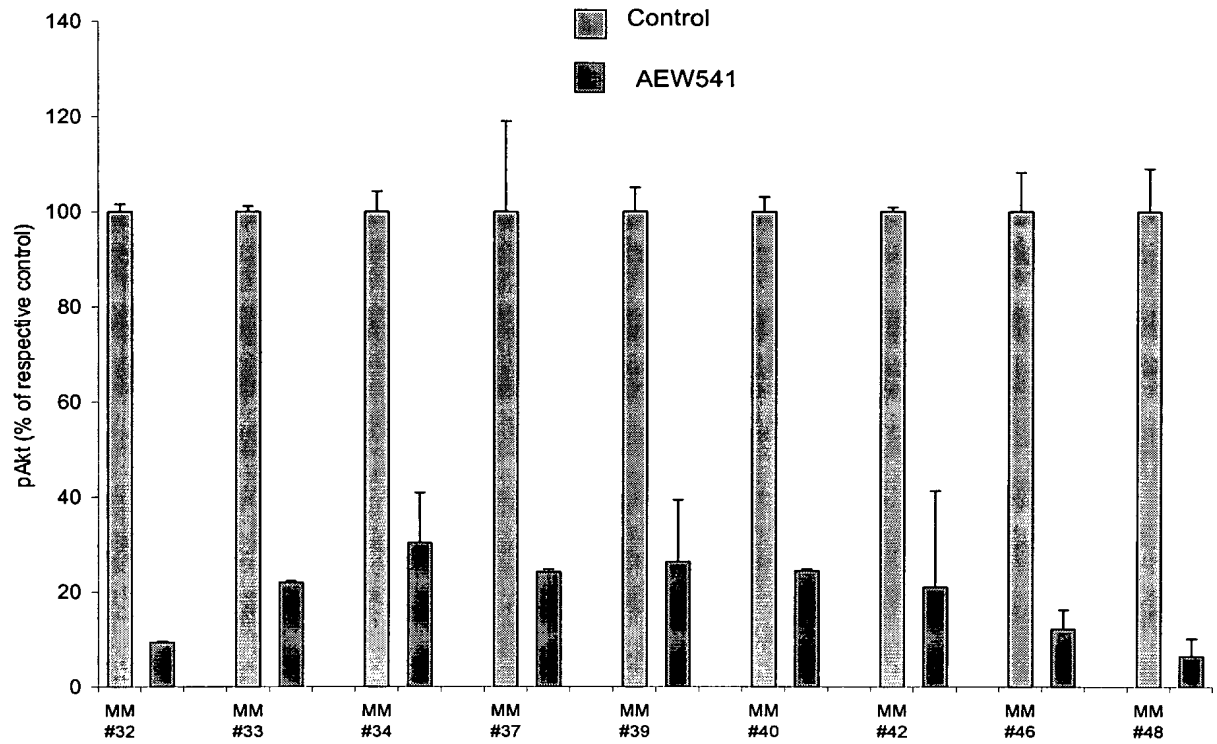


Figure 26



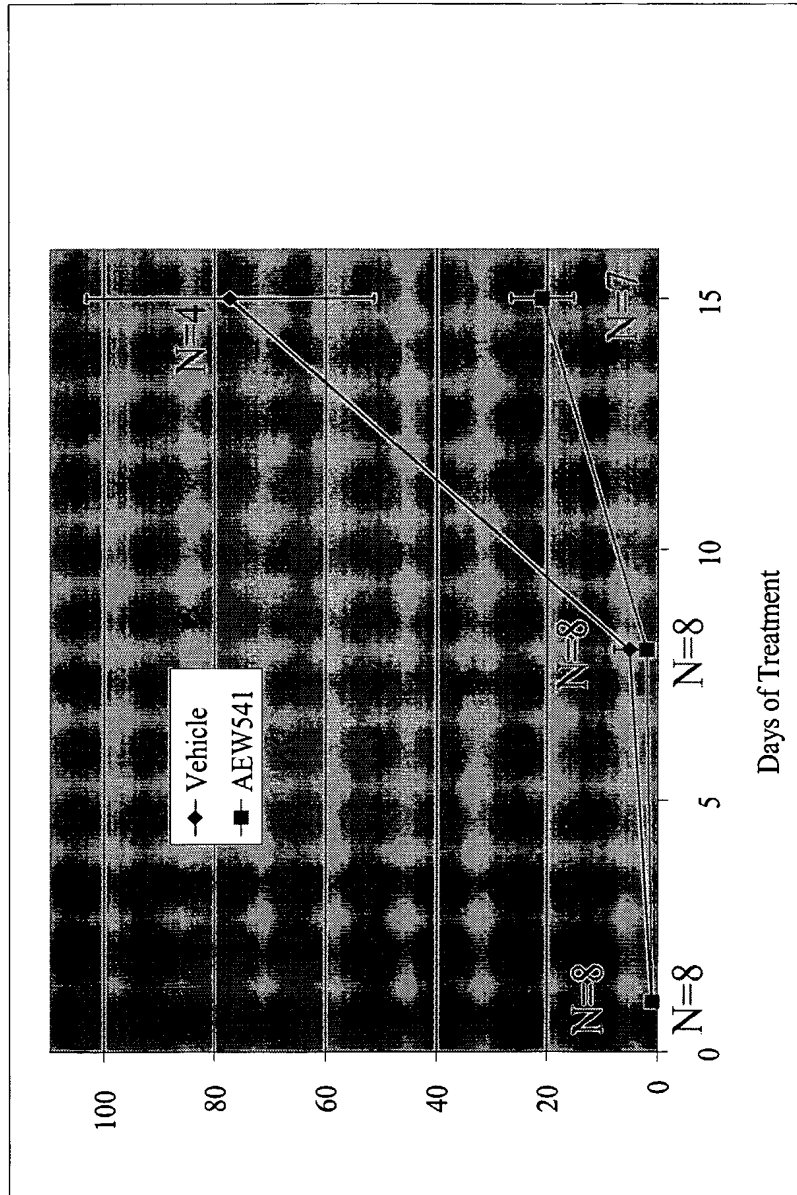


Figure 27

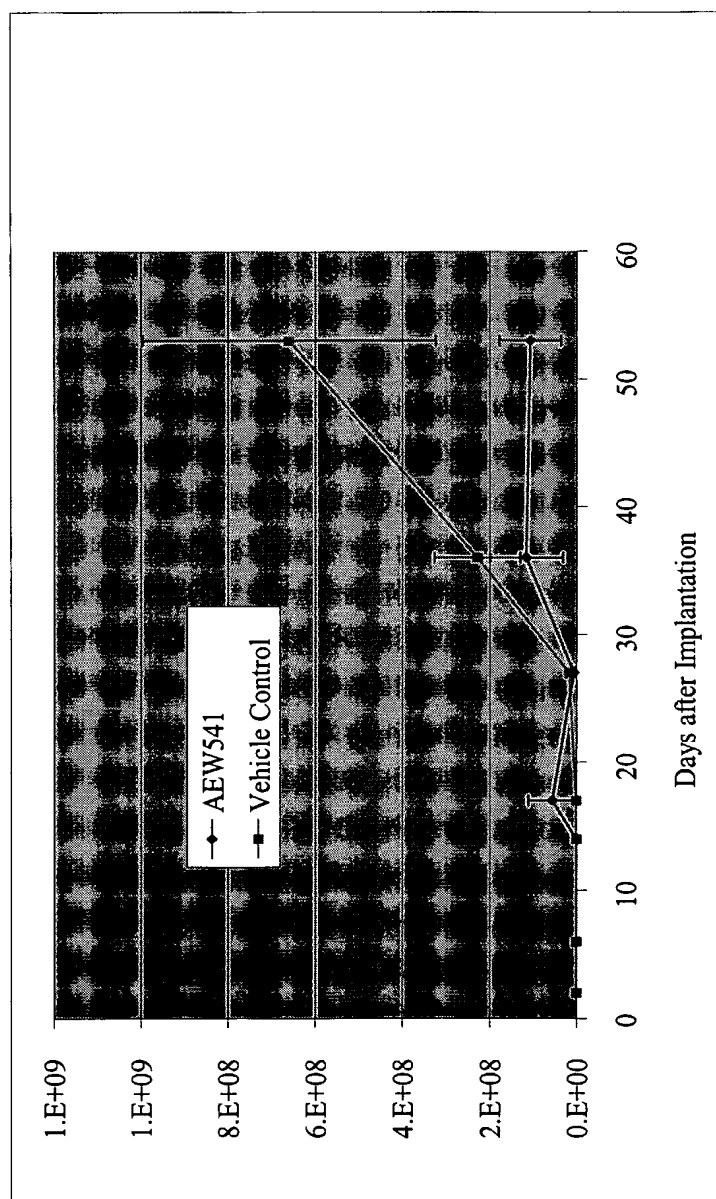


Figure 28

Figure 29

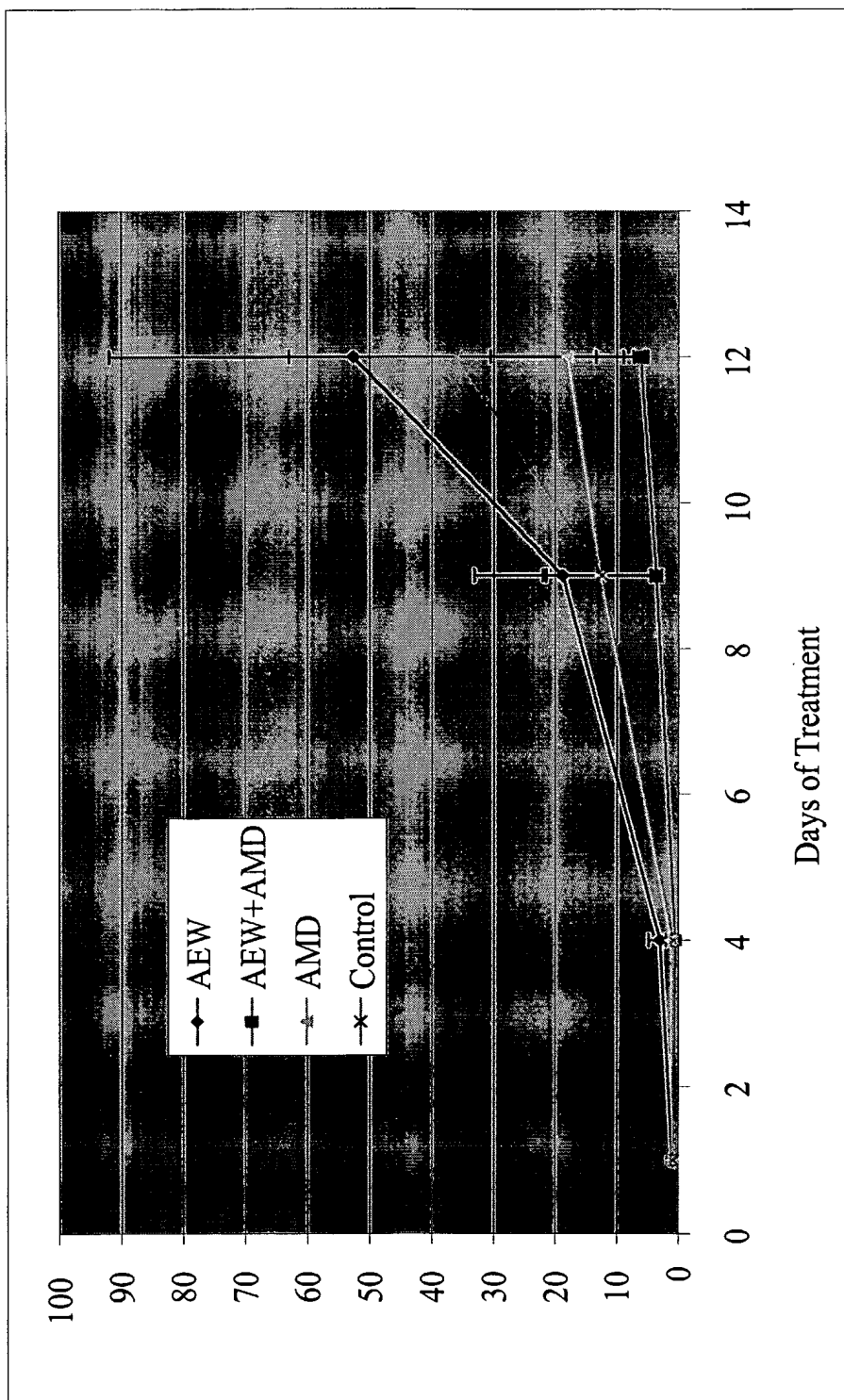
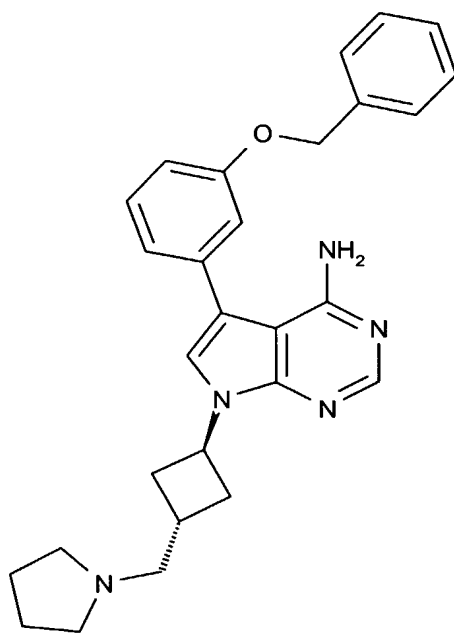
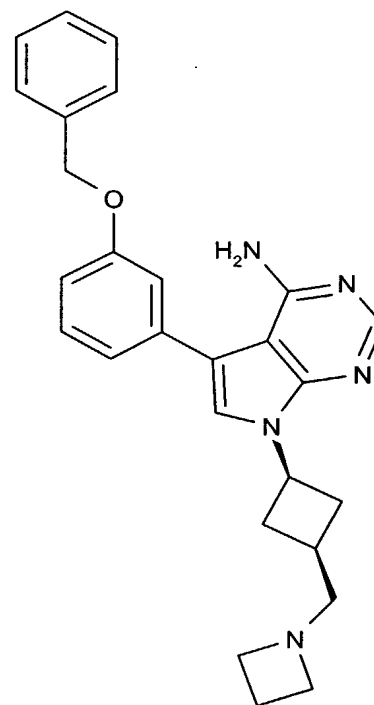


Figure 30

**ADW742**

5-(3-Benzyloxy-phenyl)-7-(3-pyrroli
din-1-ylmethyl-cyclobutyl)-7H-pyrro
lo[2,3-d]pyrimidin-4-ylamine

**AEW541**

7-(3-Azetidin-1-ylmethyl-cyclobutyl
)5-(3-benzyloxy-phenyl)-7H-pyrrolo
[2,3-d]pyrimidin-4-ylamine